CHAPTER 22
Diabetic Retinopathy

KEY TEACHING POINTS

- Three-quarters of patients with diabetic retinopathy have *normal* visual acuity.
- The findings that best predict subsequent proliferative retinopathy are venous beading, intraretinal microvascular abnormalities, and the extent of microaneurysms and hemorrhages. Soft and hard exudates are less predictive.
- Specialists using direct ophthalmoscopy are more accurate than general clinicians, and examinations through dilated pupils are superior to nondilated ones.
- Nonmydriatic digital images have proven accuracy and are commonly used to screen large numbers of diabetic patients for retinopathy.

I. INTRODUCTION

Diabetic retinopathy is the leading cause of blindness in adults between the ages of 25 and 74.[1] Whether a patient develops retinopathy depends on the type and duration of diabetes: those with type 1 diabetes have a 0% risk of proliferative retinopathy at 5 years after diagnosis, 4% at 10 years, and 50% at 20 years, whereas for those with type 2 diabetes, especially if taking insulin, the risk is 3% to 4% at the time of diagnosis, 10% at 10 years, and 20% at 15 years.[2] Once retinopathy develops, however, one of the best predictors of progression to sight-threatening retinopathy is the extent of retinopathy during the baseline examination: the higher the grade of retinopathy during the initial examination, the greater the risk of progression (Table 22.1). In type 1 diabetics, pregnancy increases the risk of progression 2.3-fold.[2]

In large cross-sectional surveys of diabetic patients seen by general practitioners, sight-threatening retinopathy (i.e., proliferative retinopathy and more severe forms of nonproliferative retinopathy) is found in 5% to 15% of patients.[6-10]

II. THE FINDINGS

The findings of diabetic retinopathy are divided into nonproliferative changes, which occur *within* the retina, and proliferative changes, which are located on the inner surface of the retina or in the vitreous.[11] The terms *background retinopathy* and *preproliferative retinopathy* are outdated and no longer recommended, having been replaced by the grades of retinopathy shown in Table 22.1. Diabetic retinopathy progresses in an orderly fashion through these grades.

A. NONPROLIFERATIVE CHANGES (FIG. 22.1)[3]

The earliest changes to appear in diabetic retinopathy are **microaneurysms**, which are distinct red, round spots less than one-twelfth the diameter of an average optic disc, or 125 μm in its longest dimension (the average optic disc is approximately 1500 μm in diameter; 125 μm is approximately the width of an average major vein at the disc margin). **Dot hemorrhages** are larger red dots with sharp borders; red spots

TABLE 22.1 Progression to High-Risk Proliferative Diabetic Retinopathy*

Grade of Baseline Retinopathy	Principal Clinical Findings	CUMULATIVE RISK (%) OF HIGH-RISK PROLIFERATIVE RETINOPATHY AT: 1 Year	5 Years
NONPROLIFERATIVE RETINOPATHY			
Mild	Microaneurysms Dot and blot hemorrhages Soft exudates	1	16
Moderate	Extensive microaneurysms and hemorrhages IRMA Venous beading	3-8	27-39
Severe	Same as moderate†	15	56
Very severe	Same as moderate†	45	71
PROLIFERATIVE RETINOPATHY‡			
	Neovascularization Preretinal/vitreous hemorrhages Fibrovascular proliferation	22-46	64-75

*High-risk proliferative retinopathy is NVD >0.25 of disc area in size, NVD <0.25 of disc area *and* vitreous or preretinal hemorrhage, OR NVE > half of disc area *and* vitreous or preretinal hemorrhage. These figures assume that the patient is untreated.
†Moderate, severe, and very severe nonproliferative retinopathy share the same fundoscopic findings, although they differ in severity (based on standardized photographs) and the number of retinal quadrants involved.[3-5]
‡Percentages are for patients whose baseline evaluation reveals proliferative retinopathy with less than high-risk characteristics.
IRMA, Intraretinal microvascular abnormalities; *NVD*, neovascularization within one disc diameter of the optic disc; *NVE*, neovascularization elsewhere (i.e., beyond one disc diameter of the optic disc); see the text.

with indistinct borders are **blot hemorrhages.** Both dot and blot hemorrhages are located in the inner retinal layers. **Hard exudates** (deposition of lipid in the inner retina) are small, white or yellowish-white deposits with sharp margins that often have a waxy or glistening appearance. **Soft exudates** (or **cotton wool exudates**) are ischemic swellings of the superficial nerve fiber layer, which appear as white, round, or oval patches with ill-defined, feathery edges. As retinal ischemia progresses, two other abnormalities appear: venous beading (veins resembling a string of beads) and intraretinal microvascular abnormalities (IRMA), which are extra tortuous vessels *within* the retina that may be either new vessels or dilated preexisting capillaries.

B. PROLIFERATIVE RETINOPATHY

Proliferative retinopathy is new vessel formation (i.e., neovascularization) on the inner surface of the retina or vitreous, which threatens vision by increasing the risk of retinal detachment or vitreous hemorrhage. These new vessels often resemble a small wagon wheel, with individual vessels radiating like spokes to a circumferential vessel forming the rim.[12] New vessel formation is subdivided into neovascularization of the disc (within one disc diameter of the optic disc, abbreviated NVD) and neovascularization elsewhere (NVE). Of the two, NVD has a much worse visual prognosis.[5]

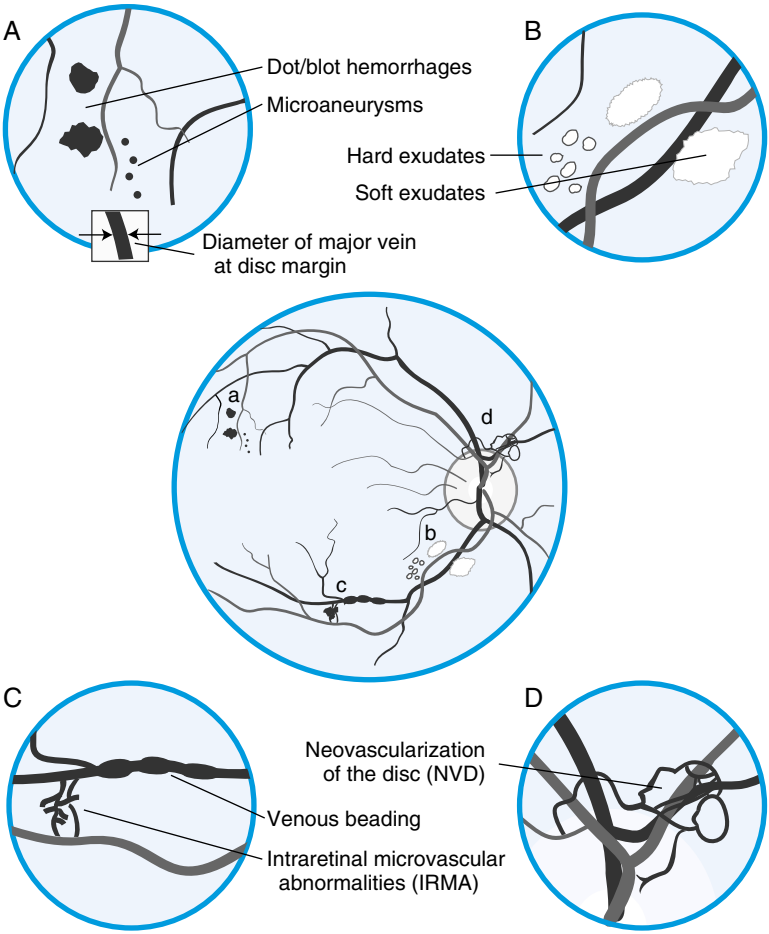

FIG. 22.1 TYPES OF DIABETIC RETINOPATHY. The center figure depicting the fundus of a patient with diabetic retinopathy is surrounded by four enlarged views, each labeled with a letter (A to D) corresponding to specific locations on the center figure. (A) Microaneurysms and dot and blot hemorrhages. The diameter of microaneurysms is less than the width of a major vein at the disc margin (reproduced in square inset). (B) Hard and soft exudates. (C) Venous beading and intraretinal microvascular abnormalities (IRMA). (D) Neovascularization, which may be located within one disc diameter of the optic disc (NVD) or elsewhere (NVE). Although both IRMA and neovascularization represent the formation of new blood vessels, IRMA are confined to the layers of the retina, whereas neovascularization is on the inner surface of the retina or vitreous. (see the text).

C. MACULAR EDEMA

Macular edema, which may accompany any stage of nonproliferative or proliferative retinopathy, is very difficult to visualize using the direct ophthalmoscope, although important clues are rings of hard exudates (often surrounding the edematous area) and diminished visual acuity.[11]

III. CLINICAL SIGNIFICANCE

In patients with high-risk proliferative retinopathy or those with clinically significant macular edema, laser photocoagulation reduces the risk of subsequent visual loss by at least 50% (the footnote of Table 22.1 defines high-risk proliferative retinopathy).[1] Retinal examination is the only way to detect these lesions, thereby making diabetic retinopathy one of the best examples of a disorder benefiting from careful, attentive physical examination.

The findings that best predict subsequent proliferative retinopathy are venous beading, IRMA, and the extent of microaneurysms and hemorrhages. Soft exudates are less predictive, and the extent of hard exudates correlates poorly with subsequent proliferative retinopathy.[5]

A. VISUAL ACUITY AND DIABETIC RETINOPATHY

Diminished visual acuity per se is a poor screening test for diabetic retinopathy (EBM Box 22.1: positive likelihood ratio (LR) = 1.5, negative LR = not significant [NS]). Indeed, the most common causes of diminished visual acuity in diabetics are cataracts (49% of diabetics with diminished acuity) and macular degeneration (29%), not diabetic retinopathy (15%).[14]

B. DIAGNOSTIC ACCURACY OF OPHTHALMOSCOPY

EBM Box 22.1 displays the accuracy of various methods in detecting sight-threatening retinopathy (i.e., proliferative changes and macular edema), using multiview dilated pupil retinal photographs or slit-lamp biomicroscopy as the diagnostic standard. Not surprisingly, specialists using direct ophthalmoscopy perform better than general clinicians, and dilated examinations are superior to nondilated ones. Many diabetic centers now routinely screen their patients for retinopathy using three-view nonmydriatic photographs, which have excellent diagnostic accuracy (see EBM Box 22.1).

Macular edema is rarely detected by general providers using direct ophthalmoscopy (sensitivity is close to 0%).[23] Because many patients with macular edema have normal visual acuity (i.e., the sensitivity of "visual acuity worse than 20/30" for macular edema is only 38%),[23] clinicians who screen for macular edema using only visual acuity are missing many patients who would benefit from laser photocoagulation.

C. SCREENING RECOMMENDATIONS

Diabetic retinopathy is common, treatable, and detectable using simple tools: consequently, it is the prototype of a disease that would benefit from organized screening. Table 22.2 reviews the screening schedule recommended by the American Diabetes Association.[1] Given the stakes of missing serious retinopathy and the less-than-optimal performance of general clinicians using only direct ophthalmoscopy, only clinicians with training and experience—in most cases optometrists and ophthalmologists—should screen patients. Any patient with macular edema, more than moderate nonproliferative retinopathy, or proliferative retinopathy should be seen by eye care providers with experience in the management of diabetic retinopathy.

EBM BOX 22.1
*Ophthalmoscopy and Diabetic Retinopathy**

Finding (Reference)†	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio‡ if Finding Is	
			Present	*Absent*
Detecting Any Diabetic Retinopathy				
Visual acuity 20/40 or worse[13,14]	21-28	82-86	1.5	NS
Detecting Sight-Threatening Retinopathy, Using the Following Technique				
Direct ophthalmoscopy, nondilated pupils[15]	50	92	**6.2**	0.5
Direct ophthalmoscopy, dilated pupils, general providers[8,9,16-18]	53-69	91-96	**9.4**	0.4
Direct ophthalmoscopy, dilated pupils, specialists[6-10]	48-82	90-100	**25.5**	**0.3**
Nonmydriatic three-view digital photographs[19-22]	71-99	93-100	**31.3**	**0.2**

*Diagnostic standard: for *sight-threatening retinopathy,* retinal photographs through dilated pupils or slit-lamp biomicroscopy reveal proliferative retinopathy, macular edema, or both.
†Definition of findings: for *sight-threatening retinopathy,* proliferative retinopathy, macular edema, or both.
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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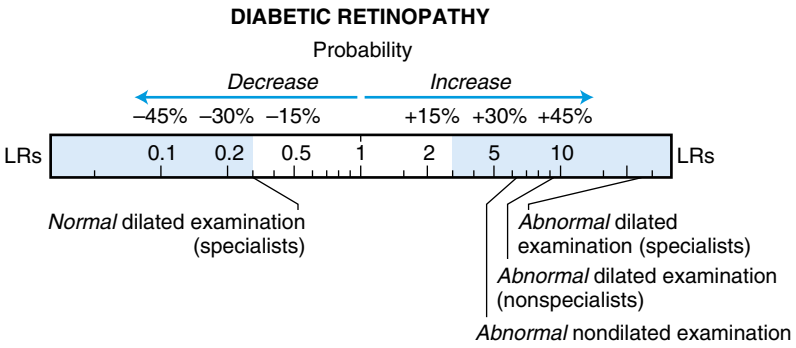

TABLE 22.2 Recommended Ophthalmologic Examination Schedule for Patients With Diabetes Mellitus

Time of Onset of Diabetes	Recommended First Examination	Minimal Routine Follow-Up
Less than 30 years of age*	Within 5 years after diagnosis of diabetes	Yearly†
30 years of age or older*	At time of diagnosis of diabetes	Yearly†
Pregnancy in preexisting diabetes	Prior to conception and during first trimester	Physician discretion pending results of first trimester examination

*Less than 30 years and greater than 30 years are operational definitions of type 1 and type 2 diabetes used in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.
†In some patients with normal eye examinations, eye specialists may advise less frequent examinations (every 2 to 3 years).[1]

The references for this chapter can be found on www.expertconsult.com.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33(suppl 1):S11–S61.
2. Singer DE, Nathan DM, Fogel HA, Schachat AP. Screening for diabetic retinopathy. *Ann Intern Med*. 1992;116(8):660–671.
3. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House Classification. ETDRS report number 10. *Ophthalmology*. 1991;98:786–806.
4. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. *Ophthalmology*. 1991;98:766–785.
5. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. *Ophthalmology*. 1991;98:823–833.
6. Moss SE, Klein R, Kessler SD, Richie KA. Comparison between ophthalmoscopy and fundus photography in determining severity of diabetic retinopathy. *Ophthalmology*. 1985;92:62–67.
7. Harding SP, Broadbent DM, Neoh C, White MC, Vora J. Sensitivity and specificity of photography and direct ophthalmoscopy in screening for sight threatening eye disease: the Liverpool diabetic eye study. *Br Med J*. 1995;311(7013):1131–1135.
8. Gibbons RL, Owens DR, Allen JC, Eastman L. Practical application of the European Field Guid in screening for diabetic retinopathy by using ophthalmoscopy and 35 mm slides. *Diabetologia*. 1998;41:59–64.
9. Buxton MJ, Sculpher MJ, Ferguson BA, et al. Screening for treatable diabetic retinopathy: a comparison of different methods. *Diabet Med*. 1991;8:371–377.
10. Emanuele N, Klein R, Moritz T, et al. Comparison of dilated fundus examinations with seven-field stereo fundus photographs in the Veterans Affairs diabetes trial. *J Diabetes Complications*. 2009;23:323–329.
11. Fonseca V, Munshi M, Merin LM, Bradrord JD. Diabetic retinopathy: a review for the primary care physician. *South Med J*. 1996;89(9):839–846.
12. Rishi P, Bhende PS. Proliferative diabetic retinopathy. *N Engl J Med*. 2009;360(9):912.
13. Ivers RQ, Macaskill P, Cumming RG, Mitchell P. Sensitivity and specificity of tests to detect eye disease in an older population. *Ophthalmology*. 2001;108:968–975.
14. Scanlon PH, Foy C, Chen FK. Visual acuity measurement and ocular co-morbidity in diabetic retinopathy screening. *Br J Ophthalmol*. 2008;92:775–778.
15. Klein R, Klein BE, Neider MW, Hubbard LD, Meuer SM, Brothers RJ. Diabetic retinopathy as detected using ophthalmoscopy, a nonmydriatic camera and a standard fundus camera. *Ophthalmology*. 1985;92:485–491.
16. O'Hare JP, Hopper A, Madhaven C, et al. Adding retinal photography to screening for diabetic retinopathy: a prospective study in primary care. *Br Med J*. 1996;312:679–682.
17. Owens DR, Gibbins RL, Lewis PA, Wall S, Allen JC, Morton R. Screening for diabetic retinopathy by general practitioners: ophthalmoscopy or retinal photography as 35 mm colour transparencies? *Diabet Med*. 1998;15(2):170–175.
18. Ahsan S, Basit A, Ahmed KR, et al. Diagnostic accuracy of direct ophthalmoscopy for detection of diabetic retinopathy using fundus photographs as a reference standard. *Diabetes Metab Syndr*. 2014;8:96–101.
19. Bursell SE, Cavallerano JD, Cavallerano AA, et al. Stereo nonmydriatic digital-video color retinal imaging compared with early treatment diabetic retinopathy study seven standard field 35-mm stereo color photos for determining level of diabetic retinopathy. *Ophthalmology*. 2001;208:572–585.
20. Vujosevic S, Benetti E, Massignan F, et al. Screening for diabetic retinopathy: 1 and 3 nonmydriatic 45-degree digital fundus photographs vs 7 standard early treatment diabetic retinopathy study fields. *Am J Ophthalmol*. 2009;148:111–118.
21. Lopez-Bastida J, Cabrera-Lopez F, Serrano-Aguilar P. Sensitivity and specificity of digital retinal imaging for screening diabetic retinopathy. *Diabet Med*. 2007;24:403–407.
22. Murgatroyd H, Ellingford A, Cox A, et al. Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. *Br J Ophthalmol*. 2003;88:920–924.
23. Nathan DM, Fogel HA, Godine JE, et al. Role of diabetologist in evaluating diabetic retinopathy. *Diabetes Care*. 1991;14:426–433.